

We claim:

1. A method of reducing the complexity of a nucleic acid sample comprising:  
fragmenting the nucleic acid sample using a first and second restriction enzyme to  
5 produce fragments;  
ligating adaptors to the fragments; and  
selectively amplifying the fragments that were cut on one end by the first  
restriction enzyme and on the other end by the second restriction enzyme.
- 10 2. The method of claim 1 wherein the amplified fragments comprise at least 0.01%  
of the first nucleic acid sample.
3. The method of claim 1 wherein the amplified fragments comprise at least 0.5% of  
the first nucleic acid sample.
- 15 4. The method of claim 1 wherein the amplified fragments comprise at least 3% of  
the first nucleic acid sample.
5. The method of claim 1 wherein the amplified fragments comprise at least 12% of  
20 the first nucleic acid sample.
6. The method of claim 1 wherein the amplified fragments comprise at least 30% of  
the first nucleic acid sample.
- 25 7. The method of claim 1 wherein the amplified fragments comprise at least 50% of  
the first nucleic acid sample.
8. The method of claim 1 wherein the first restriction enzyme has a six base pair  
recognition sequence and the second restriction enzyme has a four base pair recognition  
30 sequence.

9. The method of claim 1 wherein the first restriction enzyme has an eight base pair recognition sequence and the second restriction enzyme has a four base pair recognition sequence.

5 10. The method of claim 1 wherein the fragments are amplified by PCR.

11. The method of claim 1 wherein the nucleic acid sample is genomic DNA, DNA, cDNA derived from RNA, total RNA or mRNA.

10 12. The method of claim 1 wherein ligation of one strand of each adaptor is blocked.

13. The method of claim 12 wherein ligation is blocked by introducing a gap of at least one nucleotide between one strand of the adaptor and one strand of the fragment.

15 14. The method of claim 12 wherein ligation is blocked by the absence of a phosphate at the 5' end of an adaptor strand.

15. The method of claim 12 wherein ligation is blocked by the presence of a modified nucleotide at the 5' or 3' end of an adaptor strand.

20 16. The method of claim 12 wherein ligation is blocked by a terminal modification in one strand of an adaptor.

25 17. The method of claim 12 wherein ligation is blocked at the 5' end of one strand of one adaptor and at the 3' end of one strand of the other adaptor.

18. The method of claim 12 wherein ligation is blocked at the 5' end of one adaptor and at the 3' end of the other adaptor.

19. The method of claim 1 wherein one adaptor comprises a 5' overhang comprising a primer binding site and the other adaptor comprises a 3' overhang comprising a primer binding site.

20. A method for analyzing a nucleic acid sample comprising:  
fragmenting the nucleic acid sample using a first and second restriction enzyme to produce fragments;

ligating adaptors to the fragments;

selectively amplifying the fragments that were cut on one end by the first

restriction enzyme and on the other end by the second restriction enzyme;

providing a nucleic acid array;

hybridizing the amplified fragments to the array; and

analyzing a hybridization pattern resulting from the hybridization.

21. The method of claim 20 wherein the method for analyzing the nucleic acid sample comprises determining whether the nucleic acid sample contains sequence variations.

22. The method of claim 21 wherein the sequence variations are single nucleotide polymorphisms (SNPs).

23. The method of claim 20 wherein the nucleic acid array is designed to query DNA fragments which have been produced by the procedures used to obtain the amplified fragments.

24. The method of claim 20 wherein a substantial amount of the sequences predicted to be contained in the amplified fragments are first determined by a computer system.

25. A method of screening for DNA sequence variations in an individual comprising:  
providing a nucleic acid sample from the individual;

fragmenting the nucleic acid sample using a first and second restriction enzyme to produce fragments;

ligating adaptors to the fragments; and  
selectively amplifying the fragments that were cut on one end by the first  
restriction enzyme and on the other end by the second restriction enzyme;  
providing a nucleic acid array;  
5 hybridizing the amplified fragments to the array;  
generating a hybridization pattern resulting from the hybridization; and  
determining the presence or absence of DNA sequence variations in the individual  
based upon an analysis of the hybridization pattern.

- 10 26. The method of claim 25 wherein the sequence variation is at least one single  
nucleotide polymorphism (SNP).
27. The method of claim 26 wherein the at least one SNP is associated with a disease.
- 15 28. The method of claim 26 wherein the at least one SNP is associated with the  
efficacy of a drug.
29. A method of screening for DNA sequence variation in a population of individuals  
comprising:
- 20 providing a first nucleic acid sample from each of the individuals;  
providing a second nucleic acid sample by:  
fragmenting the first nucleic acid sample using a first and second restriction  
enzyme to produce fragments;  
ligating adaptors to the fragments; and  
25 selectively amplifying the fragments that were cut on one end by the first  
restriction enzyme and on the other end by the second restriction enzyme;  
providing a plurality of identical nucleic acid arrays wherein the arrays comprise  
probes designed to interrogate for DNA sequence variations;  
hybridizing each of the second nucleic acid samples to one of the plurality of  
30 identical arrays;

generating a plurality of hybridization patterns resulting from the hybridizations;  
and  
analyzing the hybridization patterns to determine the presence or absence of  
sequence variation in the population of individuals.

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30. The method of claim 29 wherein the sequence variation is at least one single  
nucleotide polymorphism (SNP).

31. The method of claim 27 wherein the at least one SNP is associated with a disease.

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32. The method of claim 27 wherein the at least one SNP is associated with the  
efficacy of a drug.

33. A method of genotyping an individual comprising:

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providing a first nucleic acid sample from the individual;

providing a second nucleic acid sample by:

fragmenting the first nucleic acid sample using a first and second restriction  
enzyme to produce fragments;

ligating adaptors to the fragments; and

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selectively amplifying the fragments that were cut on one end by the first  
restriction enzyme and on the other end by the second restriction enzyme;

hybridizing the second nucleic acid sample to an array designed to determine the  
presence or absence of one or more alleles of a collection of SNPs;

generating a hybridization pattern resulting from the hybridization; and

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determining the presence or absence of the one or more alleles of the collection of  
SNPs.

34. A kit for reducing the complexity of a nucleic acid sample comprising:

buffers and restriction enzymes for fragmenting a nucleic acid sample,

a ligase and adaptors to be ligated to the fragments, the adaptors being designed for the selective amplification of the fragments that were cut on one end by a first restriction enzyme and on the other end by a second restriction enzyme,

primers for the selective amplification, and

5 instructions for the use of the kit.

TOPEX "TECHNOLOGY"